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Synthesis, characterization and crystallographic analysis of *N*-2-(tert-butylcarbomyl) (4-chlorophenyl methyl)-6-fluoro-*N*-(3, 4, 5-triethoxyphenyl) chroman-2-carboxamide

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The title compound (UGCl 001) has been prepared by the multicomponent reaction of chromanes (U-4CC) without using catalyst. The compound has been characterized by ^{1}H and ^{13}C NMR, IR and MS techniques. X-ray crystallographic technique has been applied and the results show that the crystal belongs to the triclinic system having space group P-1(#2) with unit cell parameters, a = 10.704(2) Å, b = 12.843(2) Å, c = 13.179(2) Å, α = 116.968(4)°, β = 103.203(4)°, γ = 95.788(5)°, V = 1527.8(4) Å^3 and Z = 2. In the title compound, dihedral angles between the planes of the chromane ring (A), substituted aniline ring (B), substituted benzaldehyde (C) and *tert*-butyl isocynides (D) are 121.2 (3), 123.0(2) and 113.0(3) respectively. Intermolecular N---O, C---Cl and C---F interaction has been found in the crystal structure and results in a three dimensional network structure.

Keywords: Chromane, crystal structure, X-ray diffraction analysis

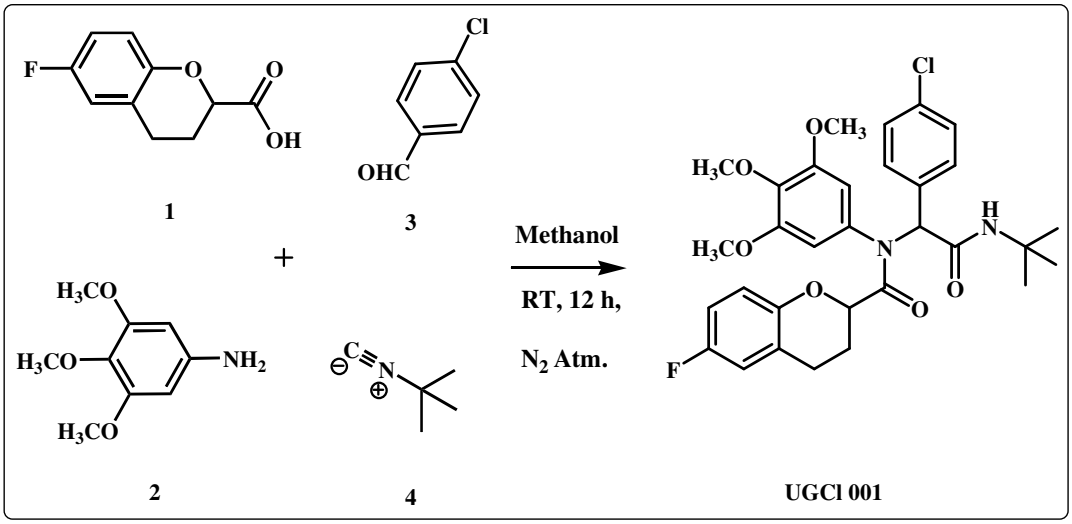
In recent, Chromanes and its derivatives are an important pharmacophore in modern drug discovery due to their various biological and pharmaceutical properties like antibacterial, antifungal, antidiabetic, antiviral, antitumor, antihypertensive, etc[1-7]. By literature and docking study results has been given more attention to the chromene nucleus as a source of new antitubercular agent[8-10]. The knowledge gained by various researches has been suggested that substituted chromane ring, which interact easily with the receptors and possess different pharmacological activities with lower toxicity. As our purpose to obtain some new antitubercular agent with low toxicity was synthesized and its structural orientation was reported here.

Experimental Section

All research chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co, Merck Chemicals, Finar and Spectrochem Ltd and used as received. Melting point was measured by open capillary method. Infrared (IR) spectra were recorded on Shimadzu IR Affinity-1S spectrophotometer over frequencies ranging from 4000-400 cm^{-1}. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker Advance Spectrospin 400 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as a solvent. Mass spectrum was obtained with Shimadzu GCMS-QP 2010 mass spectrometer using Electron Impact (EI) (0.7 kV) ionization source. The ion source temperature was 220°C and interface temperature was 220°C (Scheme I).

Preparation and crystallization of title compound (UGCl 001)

In a methanol containing flask, add 6-fluorochroman-2-carboxilic acid (0.017 mole), 3,4,5-trimethoxyaniline (0.017 mole), 4-chlorobenzaldehyde (0.017 mole) and *tert*-butyl isocyanides (0.018 mole) which was stirred at RT for 12.0 hr. Reaction was monitored by TLC using hexane: ethyl acetate as a mobile phase. After completion of the reaction, the reaction mixture was poured into crushed ice water and stirred at RT for a further 12.0 hours. The precipitation formed was filtered and washed with cold water and dried it for further purification. The crude product was purified by recrystallization using ethanol. Final purification was carried out by silica gel column chromatography using ethyl acetate: hexane (80: 20) as a mobile phase. Good quality of single crystals was obtained by slow evaporation of chloroform: methanol (1: 1) solvent system.



Scheme I — Preparation of the title compound (UGCl 001)

Spectral data of compound (UGCl 001)

Yield 68%. m.p. 220°C. IR: 3323 (NH- Stretching), 2937 (C-H Stretching), 1672 & 1645 (Amidic C=O Stretching), 1548 (Ar-C=C Stretching), 1492 & 1319 (C-H Bending), 1257 (C-O Bending), 1115 (C-F Stretching), 997 (*p*-disubstituted), 798 cm^{-1} (C-Cl Stretching); ^1H NMR ($CDCl_3$): δ 7.19-7.17 (d, 2H, J = 7.17 H_z), 7.14-7.10 (d, 2H, J = 7.12 H_z), 6.97-6.95 (d, 2H, J = 6.95 H_z), 6.69-6.09 (m, 3H), 5.71 (s, 1H), 5.41 (s-broad, 1H), 4.53-4.50 (m, 1H), 3.81-3.78 (d, 3H, J = 3.8 H_z), 3.75-3.71 (m, 6H), 2.74-2.56 (m, 2H), 2.14-2.02 (m, 2H), 1.26 (s, 1Hc); ^{13}C NMR ($CDCl_3$): δ 170.46, 162.76, 160.95, 158.45, 155.68, 152.08 (d), 140.29, 136.73, 135.32, 130.62, 128.65, 127.94, 122.60 (d), 114.71 (d), 113.18, 112.97, 111.26, 111.06, 106.35, 77.95, 62.36, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80; MS: *m/z* 585 [M^+].

X-RAY crystallographic details of UGCl 001

A colorless chip shaped crystal with approximate dimensions of 0.760 × 0.620 × 0.300 mm^3 was used for X-ray diffraction study. The measurements were carried out on a Rigaku SCX mini diffractometer using graphite monochromated Mo-Kα radiation (λ= 0.71075 Å). The diffraction data were collected at a temperature of 20°C to maximum 2θ value of 55.0°. A total of 15580 reflections was measured, out of which 6966 were found unique (R_{int} = 0.0294); equivalent reflections were merged. Data were collected and processed using Crystal Clear software (Rigaku)[11]. The reflection data were corrected for Lorentz and polarization effects and no absorption correction was applied. The structure was solved by direct methods

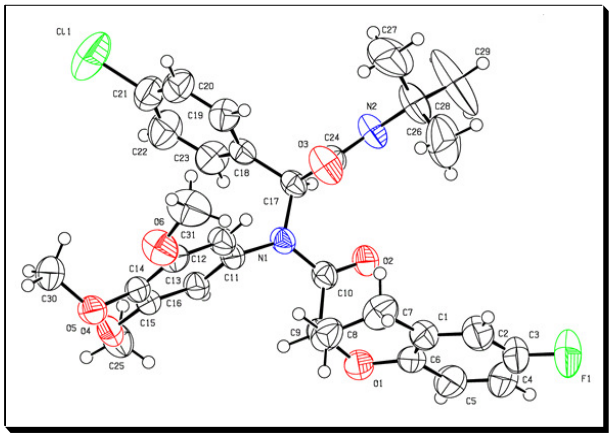


Figure 1 — Molecular structure of title compound displacement ellipsoid plot drawn at the 50% probability level, showing the complete atom labelling

using SHELXD[12] and refined by full matrix least squares method by using SHELXL-97[13] with anisotropic displacement parameter for all non H-atoms. Refinement of 370 parameters with 6966 unique reflections converged the residuals to R_1 = 0.0602. The electron density (Δρ) in the final difference Fourier map ranges from 0.26 to –0.27 $e^-/Å^3$. The value of F (000), *i.e.* the total number of electrons per unit cell, is 616 and goodness of fit on F^2 was 0.782. The crystal data and structural refinement are listed in Table I. ORTEP diagram of the molecules is shown in Figure 1.

Results and Discussion

Crystal Structure and its Refinements

Selected bond distances and bond angles are listed in Table II. Selected torsion angles are given in Table III.

Table I — Crystal data and Structure Refinement

Deposition Number	1402769
Empirical Formula	$C_{31}H_{34}ClFN_2O_6$
Formula Weight	585.07
Crystal Colour, Habit	Colorless, Chip
Temperature (k)	293 K
Wavelength (Å)	0.71075 Å
Crystal System	Triclinic
Crystal Dimensions (mm^3)	$0.760 \times 0.620 \times 0.300$ mm^3
Lattice Type	Primitive
Unit Cell dimensions (Å)	a = 10.704(2) Å, α = 116.968(4) ° b = 12.843(2) Å, β = 103.203(4) ° c = 13.179(2) Å, γ = 95.788(5) °
Volume ($Å^3$)	V = 1527.8(4) $Å^3$
Z value	2
Calculated Density (g/cm^3)	1.272
Absorption Coefficient	1.753 cm^{-1}
F(000)	616.00
$2\theta_{max}$	55.0°
Θ range	3.4 – 27.5°
Reflections Measured/ Unique	15580/6966 [R_{int} = 0.0294]
Structure solution	SHELXD Direct method
Refinement	Full matrix least-squares on F^2
Data/restrains/variables	6966/0/370
Goodness of Fit indicator	0.782
R indices (All reflections)	0.0976
$_wR_2$ (All reflections)	0.2450
R_1 (I>2.00 σ(I))	0.0602
Maximum peak in final diff. map ($e^-/Å^3$)	0.26 $e^-/Å^3$
Minimum peak in final diff. map ($e^-/Å^3$)	−0.27 $e^-/Å^3$

Table II — Selected bond lengths (Å) and bond angles

Bond Lengths (Å)

Atoms	Distance	Atoms	Distance
Cl1 - C21	1.738(5)	F1 - C3	1.353(6)
O2 – C10	1.214(3)	O3 – C24	1.214(4)
O4 – C25	1.412(4)	O5 – C30	1.406(6)
O6 – C31	1.393(5)	N1 - C10	1.358(5)
N1 – C11	1.440(3)	N1 - C17	1.482(3)
N2 – C24	1.327(3)	N2 – C26	1.469(4)
C2 – C3	1.361(8)	C5 – C6	1.376(6)
C11 – C12	1.370(4)	C13 – C14	1.396(4)
C17 – C18	1.513(5)	C17 – C24	1.531(4)
C18 – C19	1.378(5)	C22 – C23	1.371(7)

Bond Angles (°)

Atoms	Angle	Atoms	Angle
C10-N1-C11	123.0(2)	C1-C2-C3	119.1(4)
C1-C6-C5	122.1(4)	C1-C7-C8	111.1(4)
C7-C8-C9	110.5(3)	O1-C9-C8	110.0(3)
C12-C11-C16	122.0(2)	C13-C14-C15	119.6(2)
C18-C17-C24	113.0(3)	C19-C18-C23	117.2(4)
C21-C22-C23	119.6(4)	O3-C24-N2	124.7(3)
C27-C26-C28	109.4(5)	C27-C26-C29	111.5(4)
C28-C26-C29	109.5(5)		

Table III — Torsion Angles (°)

Atoms	Angle	Atoms	Angle
C25-O4-C15-C16	−5.9(5)	C30-O5-C14-C13	77.5(4)
C31-O6-C13-C12	14.5(5)	C10-N1-C11-C12	103.5(3)
C10-N1-C11-C16	−77.2(4)	C1-C2-C3-F1	−179.4(3)
C18-C17-C24-N2	−100.3(3)	C24-C17-C18-C23	159.52(15)
C19-C20-C21-Cl 1	−178.9(2)		

The bond distances and bond angles of the title compound are in a good agreement with standard values. In the title compound, central nitrogen atom (N1) and carbon atom (C17) carries four different ring systems, chromane ring (A), substituted aniline (B), substituted benzaldehyde (C) and *tert*-butyl isocyanides (D) systems. Ring system A and B is attached to a central nitrogen atom (N1), while C and D are attached to a central carbon atom (C17). The distance between N1-C17 is 1.482 Å which is nearly same that of a typical C-N bond (1.47 Å). The chromane ring (A) and substituted aniline (B) are twisted as compared to the substituted benzaldehyde (C) and *tert*-butyl isocyanides (D) systems with dihedral angle 123.04 and 112.98°, which indicates all the four systems are non-planner with each other.

In the system A and B, distances between N1-C10 and N1-C11 are 1.358 Å and 1.440 Å respectively. The torsion angle between C10-N1-C11-C12 and C10-N1-C11-C16 are 103.5(3) and -77.2(4) respectively, which also indicates that both the systems are placed in different planes with greater puckering observed at C11 than C10. Similarly, system C and D having distances between C17-C18 is 1.513 Å and C17-C24 is 1.531 Å respectively. The torsion angle between C23-C17-C18-C23 and C18-C17-C24-N2 are 159.52 (1) and -100.3(3) respectively, which also indicate that both the ring systems are non-planer with greater puckering observed at C24 than C18.

In systems A, B and C, benzene ring having a interatomic distances 1.361(8) Å for C2-C3, 1.376(6) Å for C5-C6, 1.370(4) Å for C11-C12, 1.396(4) Å for C13-C14, 1.378(5) Å for C18-C19 and 1.371(7) Å for C22-C23 are nearly same that of a typical C=C bond (1.34 Å). The bond angles between C1-C2-C3, C1-C6-C5, C12-C11-C16, C13-C14-C15, C19-C18-C23, and C21-C22-C23 are 119.1(4)°, 122.1(4)°, 122.0(6)°, 119.6(2)°, 117.2(4)°, and 119.6(4)° respectively are nearly same from the expected value of 120° sp^2 hybridization. The six member pyran ring in system A (C9-O1-C6-C1-C7-C8) adopts a stable chair like conformation. The bond angles between C1-C7-C8, C7-C8-C9, and O1-C9-C8 are 111.1(4)°, 110.5(3)°

and 110.0(3)° respectively. And its find nearly the same values to 109°, which further indicates that the carbon atoms in pyran ring adopts sp^3 hybridization.

The carbonyl and chlorine groups having an interionic distances between C10-O2, C24-O3 and Cl-C21 are 1.214(3), 1.214(4) and 1.738(5) Å respectively, which are similar to the standard value [1.21 Å for C=O and 1.73 ÅC-Cl]. But in the methoxy group containing phenyl ring, the C31-O6, C30-O5, C25-O4 bond length [1.394(5), 1.406(6) and 1.412(4)] are significantly lager than single C-O (1.34 Å) might be attributed to the steric repulsion between the aromatic rings and methoxy group. The bond length value of C3-F1 = 1.353(6) is slightly shorter than the standard value [1.37 Å for C-F], indicating an attraction of benzene ring electrons towards the fluorine atom.

Orientation of fluorine and chlorine atoms lies in the main plane of the system A and C. Similarly out of three ether group, two group lies in the main plane of system B, while one group lies in out of the plane that can be confirmed by measurement of the torsion angle value. The torsion angle value of C1-C2-C3-F1, C19-C20-C21-Cl1, C25-O4-C15-C16 and C31-O6-C13-C12 are -179.4(3), -178.9(2), -5.9(5) and 14.5(5) which is close to 0° corresponds to *synperiplanar* configuration while torsion angle C30-O5-C14-C13 is 77.5 (5), which is close to 180° corresponds to *antiperiplaner* configuration]. In amide system (C), bond length N2-C24 [1.327(3) Å] is significantly shorter than N2-C26 [1.469(4) Å] indicating a conjugation between O3-C24-N2. This can be also confirmed by measurement of the bond angle value of O3-C24-N2 is 124.67(3) that are nearly same to 120°, which indicates the N2 adopts sp^2 hybridization. The bond angle values of C27-C26-C28, C28-C26-C29 and C27-C26-C29 are 109.4(5)°, 109.5(5)°, 111.5(4)°, which are similar to standard bond value indicates that the three methyl groups are attached with carbon (C26) is sp^3 hybridized.

Detailed geometrical parameters for intermolecular interactions are listed in Table IV. The molecules are packed *via* intermolecular N2---O2(2) and O2---N2(2) interactions leading to chains parallel to ***a***- axis. These interactions results between the nitrogen of amide group and oxygen of carbonyl group of chromane ring with distances 3.018(3) Å shows in Figure 2. The resulting chains are also involved in other type of interaction H-C----F due to interactions between electron deficient carbon of ring system B and electron rich fluorine atom. The intermolecular distances C30-F1 is 3.037 Å leading to layers in the ***ab*** plane as depicted in Figure 3. All these intermolecular interactions are depicted in Figure 4.

Table IV — Hydrogen bond parameters (Å)

D-H---A	H---A	D-H	D….A	D-H…A
N2-H2-O2	2.21	0.86	3.018(3)	156.30

Symmetry Operators: -X+2, -Y+1, -Z+1

Electronic Supplementary Data

Supplementary material CCDC: **1402769** contain the supplementary crystallographic data for this paper. These data can be free of charge at www.ccdc.cam.ac.uk/dopsite/. or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: deposite@ccdc.cam.ac.uk.

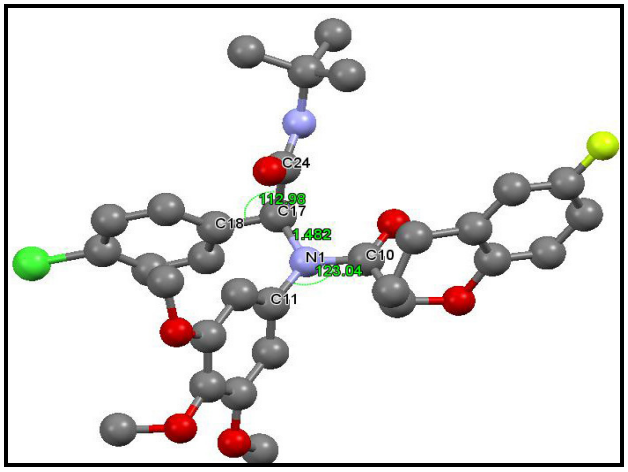


Figure 2 — Attachment of ring system A and B with N1 while C and D with C17 and distance between N1-C17 is 1.482 Å. The value of dihedral angle between C11-N1-C10 is 123.04 and C18-C17-C24 is 112.98°

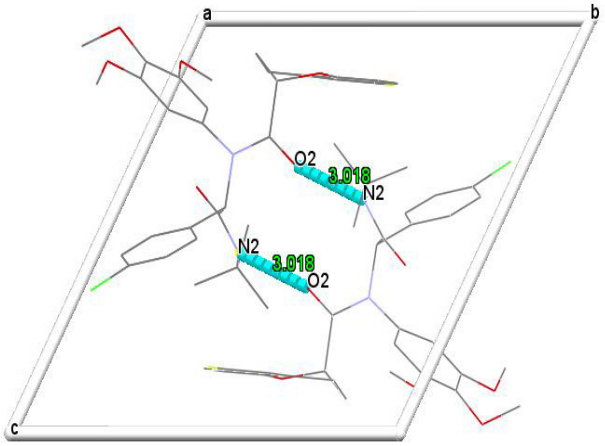


Figure 3 — The intermolecular interaction [N—H---O] are shown with symmetry operation -X+2,-Y+1,-Z+1

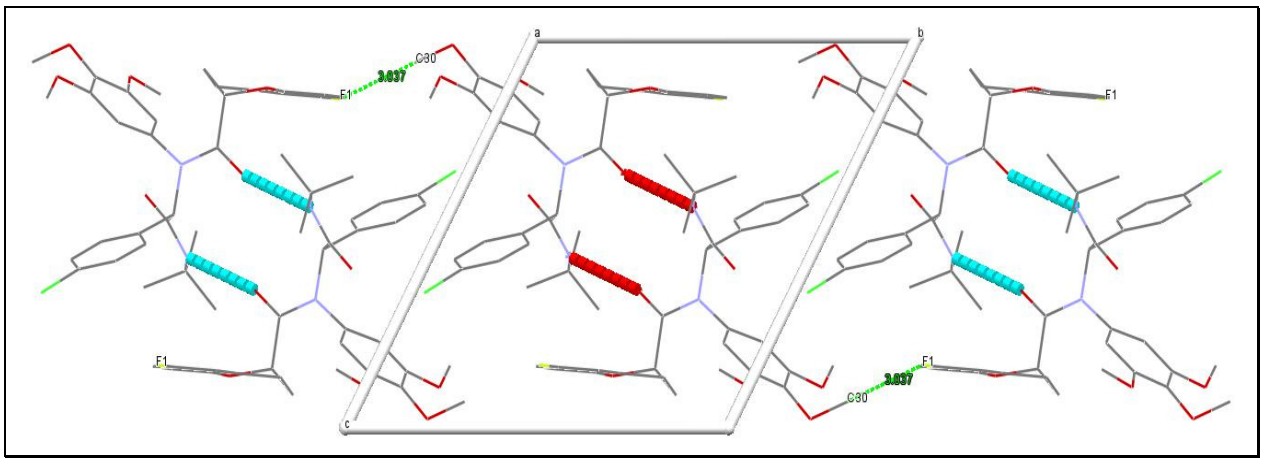


Figure 4 — Packing diagram of the title compound with intermolecular N-H—O hydrogen bond and stacking interaction *via* C30. F1 are shown viewed down the b-axis

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Conflict of interest statement

Authors declare that there is no any conflict of interest.

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